B

Appendix

TREATMENT OF ENVIRONMENTALLY SENSITIVE PATIENTS WITH TRANSFER FACTOR PART I: IMMUNOLOGIC STUDIES

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ABSTRACT

Delayed cutaneous hypersensitivity or cell-mediated immunity (CMI) to seven antigens by 25 patients and the number of T lymphocytes and T cell subsets in 18 patients were measured before and after a course of therapy with transfer factor (TF). The mean number of positive reactions by the patients to the CMI test was 1.36 before and 3.4 after TF therapy. The mean average reaction size was 5.2mm prior to and 15.54mm post therapy. The mean increase in the number of lymphocytes was 803, the number of total T cells was 718 and for the T helper cells it was 519, all statistically significant increases. The large majority of sensitive patients, 88% with or 78.5% without immunologic abnormalities, treated with TF demonstrated improvement in their clinical status. This study demonstrates possible use of TF to correct certain immunologic abnormalities observed in environmentally sensitive individuals. *Transfer Factor, T cells, cellular immune response, T & B lymphocytes, cell mediated immunity.*

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INTRODUCTION

Transfer factor (TF) is one of many biologically active components in dialysates of human leukocyte extracts (DLE). In addition to transfering antigen-specific delayed type hypersensitivity (DTH) in vivo (1,2) and CMI in vitro (3), crude leukocyte dialysates contain substances that have antigen-independent or non-specific effects on immunologic and inflammatory responses (4). These effects include the enhancement of T-cell responses to mitogens (5,6), increases in the percentage and total numbers of circulating T-lymphocytes and T-helper cells (7,8). Other components of TF include T lymphocyte maturation or differentiation factors or thymic hormones (9) as well as prostaglandins (10), histamine, serotonin, ascorbic acid, chemoattractants for monocytes and neutrophil immobilizing factors (4,11).

Despite the findings that human TF contains covalently linked peptide and ribonucleotide components (12), the nature of human TF, capable of specific transfer of dermal reactivity, is defined more in functional or biological, rather than chemical terms. To that end recently Borkowsky and Lawrence (3), using the leukocyte migration inhibition (LMI) test as an in vitro assay for antigen specific activity in dialysates of human leukocyte extracts, described transfer factor as a moiety containing two opposing antigen specific activities (3). One activity which possesses an inducer or helper function is termed the inducer factor (13), and the other activity possessing suppressor function is termed the suppressor factor (14). Inducer factor functions to convert nonimmune cells to a state of antigen-specific immune reactivity in a dose-dependent fashion. The suppressor factor functions to abrogate the response of immune cells in the presence of the related antigen.

In this and subsequent papers we report the results obtained upon treatment with transfer factor of a number of mildly immune-dysregulated or immuno-deficient patients, for 6-12 months. The data indicates restoration and augmentation of immunologic responsiveness and statistically significant increases in the total number of T cells and T-helper cells.

MATERIALS AND METHODS

Transfer factor and leukocyte donors.

Peripheral blood from random normal healthy donors were obtained from a local blood bank. Isolated leukocytes were pooled, lysed, and an extract prepared by ten cycles of freezing and thawing as reported by Lawrence (11). All components of the fraction with molecular weight at 30,000 or less were isolated and adjusted so that each unit of TF represented 10^8 lymphocyte equivalents per ml.

Phenotyping

Monoclonal antibodies against pan T cells T11 (CD2), T helper cells T4 (CD4), T suppressor/cytotoxic cells T8 (CD8), and B cells B1 (CD20) were purchased from Coulter immunology (Hialeah, Florida). Peripheral blood cells obtained by venipuncture were stained either by the whole blood technique or by the use of Coulter Q-PREP Epics immunology work station (Coulter Electronics, Inc., Hialeah, Florida) according to the manufacturer's instructions. The cells were analyzed on the Epics C optical flow cytometer (Epics Division, Coulter Electronics, Hialeah, Florida). Control ranges were determined on 60 normal subjects as described (15).

Cell Mediated Immunity (CMI)

Delayed cutaneous hypersensitivity (CMI) responses to seven antigens were tested using the multitest CMI test kit (Merieux Institute, Miami, Florida) containing the following antigens: Tetanus, Diphtheria, Streptococcus, Tuberculin, Candida, Trichophyton and Proteus. The number of positive dermal reactions was read at 48 hours and the average diameter of each induration was measured in millimeters. A reaction was considered positive if the average diameter was 2mm or more.

Patient selection

Fifty patients with food allergies (16,17) and environmental sensitivities (18) were advised to adopt environmentally safe practices such as a natural gas free environment and the use of chemically less contaminated food and water. A majority of the patients had supportive antigen immunotherapy for allergic reactions to inhalants, food and/or chemical sensitivities (16,19,20) concomitant with their TF treatment.

Patient distribution

The patients were distributed into four groups. 1) Those with normal T & B lymphocyte numbers and normal CMI response. 2) Those with abnormal T & B lymphocyte numbers and abnormal CMI response. 3) Those with normal T & B lymphocyte numbers and abnormal CMI response. 4) Those with abnormal T & B lymphocyte numbers, and normal CMI response.

Patient questionnaire

Each patient was given a symptom score sheet to be filled out prior to and following 6-12 months of TF therapy. The patients were asked to respond as to frequency and severity of symptoms in the following categories: hypersensitivity reactions to incitants, cephalgia, recurrent infections, fatigue, gastrointestinal problems, depression and lack of concentration. Based on the patient's response on a scale of 1-5, each respondent was categorized as "improved" or "no change" in his/her symptoms.

TF dose

Each patient received two weekly units of TF injected subcutaneously or intramuscularly.

RESULTS

Table 1 shows the results of the number of positive reactions and average reaction sizes in 25 patients tested for CMI. The mean number of positive reactions for the 25 reactants (Table 1) was 1.36/pt. before TF treatment and 3.4/pt. after treatment, with a mean increase of 2.04 reactions/pt. These values approached the results seen in 299 normal females, who had a mean number of positive reactions of 3.5 (Data provided by Merieux Institute Inc., Lyon, France). Since 84% of the TF recipients in our study were female, we feel that this value of 3.5 reactions is acceptable as normal control value.

The mean average sum of reaction size (Table 1) for these 25 TF recipients was 5.2 mms prior to, and 15.54 mms after TF therapy, with a mean increase in reaction size of 10.34 mms. These values substantially exceed the mean reaction size of 12.2 mm demonstrated by 299 normal female reactants. (Data provided by Merieux Institute, Inc., Lyon, France). These results indicate both restoration and augmentation of immunologic responsiveness. For example, nine of the twenty-five patients who demonstrated zero dermal reactivity on CMI testing (Table 1) converted to a positive response, thus showing de novo restoration of CMI. These nine patients showed substantial increase in their reaction size after treatment, ranging from 2.0 to 20.5 mms. The rest of the reactants demonstrated augmentation of their preexisting response. Twenty-two out of 25 or 82% of the patients either converted to a positive response or augmented their original response after TF therapy.

Table 2 shows the total number of lymphocytes, total T cells (T11), T helper cells (T4), and T suppressor/cytotoxic cells (T8), pre and post TF therapy in eighteen patients. Every cell population category except T8 (see below)

increased substantially and by statistically significant numbers. The mean increase in the number of lymphocytes was 803.4 cells ($p<0.001$); in the number of total T cells, it was 718.17 ($p<0.001$) and for the T helper cells it was 519.3 ($p<0.001$). The mean increase for the T suppressor-cytotoxic cells was 113.0 which was statistically not significant ($P>0.05$), although certain patients increased their T s/c cell population substantially. It should be noted, however, that loss of 800 cells by patient no.12 statistically skews these data. Elimination of this patient's data results in mean increase of 165 T s/c cells which is statistically significant at $p<.01$.

These increases in the cell numbers were not universal. The number of lymphocytes decreased in two patients, as did the total T cells in one patient and T4 cells in another. The total number of T8 cells decreased in four patients. These decreases occurred in different patients and cell population, in an inconsistent manner, and we feel cannot be directly attributed to TF therapy.

Not every patient entering into the TF therapy program had accompanying abnormalities as defined by lymphocyte phenotyping or CMI response. In fact, the patients were distributed into four groups as explained in materials and methods. Initial immunologic data for individual patients and their overall clinical status at the termination of their TF therapy are given in Table 3, 4, 5, and 6. Depending on each symptom category, patients showed improvement or no change in their symptoms (accumulated data and more details of patient response will appear in the accompanying papers). Eleven out of 14, or 78.6% of the patients on TF who demonstrated no immunologic abnormalities (Table 3) at the start of the trials reported clinical improvement, while 3 out 14 or 21.4% perceived no change. Fifteen out of 17 or 88.2% of the patients who exhibited numerical abnormalities of their lymphocytes or T cells as well as impaired CMI response (Table 4) reported clinical improvement, while the other two (11.8%) saw no change. Of those patients who had normal numbers of lymphocytes, but had abnormal CMI response (Table 5) 10 out of 13 patients, or 77% showed improvement, while 3 out of 13, or 23%, reported no change. The sample size in the category of patients who had abnormal numbers of lymphocytes or lymphocyte subpopulations and normal CMI (Table 6) was too small for drawing statistical conclusions in the present study.

DISCUSSION

The results demonstrate that restoration of immunologic responses can be attained in certain TF recipients as demonstrated by enhanced cutaneous hypersensitivity reactions and increases in numbers of circulating lymphocytes and their subpopulations in some patients. In twenty five patients, the mean number of positive CMI skin reactions increased from 1.36 /person to 3.4/person while the mean reaction size increased from 5.2 to 15.5 mms. These values not only approached those of the normal population but rose to supranormal levels during therapy. Despite variations in the number of lymphoid cells, the mean total numbers of lymphocytes, T-cells and T-helper cells all increased by substantially significant numbers.

Increase in a subset of T cells with helper activity was observed by Fudenberg et al (21) during dialysable leukocyte extract (TF) therapy of a woman with chronic discoid lupus. Further augmentation of T-cell rosettes and restoration of T-cell functional activity (MIF, cutaneous hypersensitivity) persuant to treatment with DLE was observed in "broad spectrum" T cell immune defects e.g. Wiscott-Aldrich syndrome and in "antigen selective" defects e.g. chronic mucocutaneous candidiasis, as well as in cytomegalovirus and other infectious diseases (22).

A survey of twenty contributing normal donors for a TF preparation (25) showed donor skin reactivities to: PPD of 20-40% positive; SK-SD 20-80%; candida 50-80%; trichophytin 30-50%; mumps 20-40%; vaccinia 80-90%. This is somewhat analogous to our preparations, which were obtained from a contributing population of 30-40 donors. Since our intent was an enhancement of general immunoreactivity and not transfer of cellular immunity to a specific antigen, use of pooled leukocyte extract from a large number of contributing donors was justified. This was most likely accomplished by the transfer of random subsets of specificities for environmental bacterial and fungal antigens in the pooled normal TF.

It appears from this study that both immunologically normal (Table 3) and abnormal (Table 4) patients are responsive to TF therapy, since in each case 78.5% and 88% of the TF recipients reported improvement in one or more of their initial symptoms. These results strongly suggest that both specific and nonspecific molecules transferred from TF donors contributed to such clinical improvements.

Previous studies (23,24) have described partial purification from human dialysates of low molecular weight immunomodulators that amplify in vivo delayed dermal reactivity responses to antigens to which the donor had preexisting immunity. In contrast to human transfer factor, these modulations do not transfer particular antigen sensitivities from highly sensitive donors to nonsensitive recepients. In addition, these components of DLE exerted intradermal inflammatory response histologically resembling delayed type hypersensitivity in the absence of antigen. These modulators may be responsible for the "nonspecific" effects described.

TABLE 1
Increase in CMI After Transfer Factor Therapy

# of Patients	Number of positive Reactions			Sum of Reaction Size (mm)		
	Before Treatment	After Treatment	Increase in # of Reactions	Before Treatment	After Treatment	Increase in Reaction Size
1.	2	6	4	10	40	30
2.	1	2	1	04	06	02
3.	2	6	4	13	23	10
4.	0	4	4	00	12	12
5.	3	3	0	21	31	10
6.	0	3	3	00	12.5	12.5
7.	0	4	4	00	20.5	20.5
8.	0	1	1	00	04	04
9.	2	3	1	05	18	13
10.	1	2	1	03	11	08
11.	3	4	1	12	13.25	01.5
12.	4	6	2	18.5	36	17.5
13.	3	6	2	10	26	16
14.	0	2	2	00	06	06
15.	0	1	1	00	02	02
16.	1	3	2	07	25.25	18.25
17.	1	5	4	03	20	17
18.	0	2	2	00	08.5	08.5
19.	1	2	1	07	07	00
20.	1	3	2	07.5	10	02.5
21.	1	1	0	03	03.5	00.5
22.	1	4	3	02	26	24
23.	1	1	0	04	04.5	00.5
24.	0	4	4	00	16	16
25.	0	2	2	00	06	06
Mean	1.3	3.4 0.001	2.04	05.2	15.54 00.001	10.34

CMI In Normal Population*

Number	Mean # of Reactions	Mean Reaction Size (mm)
315 male	4.5	18.3
299 female	3.5	12.2

* Data Provided by Institute Merieux - Lyon, France.

It is not known how many DH+ cell equivalents are contained within one unit of TF, neither is it clear how the transfer of multiple specificities to the recepient is mediated. Another unknown factor in TF therapy is the producer cell, that is, the cell releasing TF upon membrane disruption. Borkowski and Lawrence (13,14), using techniques to separate lymphocyte subpopulations, found the inducer factor can be prepared from dialysates of purified T lymphocytes with helper phenotype but not from cells with suppressor phenotype. This observation was confirmed when inducer factor could also be prepared from dialysate of T cells stimulated by antigen and clonally expanded with T cell growth factor after 2 1/2 weeks in culture. The cultured cells were composed of 94% helper cells. The same authors (13,14) used similar methodology to determine that cells of suppressor phenotype were the targets of the

Increase In N[...]bers of Lymphocytes and T Cells After [T]ransfer Factor Therapy

[...]ents	Lymphocytes 1,600-4,200/mm3 Before	After	Change	T11 1,260-2,650/mm3 Before	After	Change	T4 670-1,800/mm3 Before	After	Change	T8 33-1,070/mm3 Before	After	Change
	1602	1166	-436	0849	0968	0119	0465	0445	-020	0208	0387	0179
	1200	2669	1469	0960	2321	1361	0528	1281	0753	0408	0667	0259
	0976	3136	2160	0625	2415	1790	0439	1850	1411	0185	0439	0254
	0728	1470	0742	0648	1294	0646	0495	0853	0358	0102	0235	0133
	1050	2016	0966	0998	1848	0850	0410	0806	0396	0462	0770	0308
	1400	1591	0191	0980	1177	0197	0588	0668	0080	0392	0509	0117
	0775	2888	2113	0636	2340	1704	0450	1530	1080	0163	0491	0328
	1040	2200	1160	0645	1804	1159	0593	1276	0683	0177	0462	0285
	1368	1805	0437	1259	1679	0420	0809	1119	0310	0315	0487	0172
0.	1140	1980	0840	0969	1485	0516	0422	0693	0271	0308	0653	0345
1.	1656	1914	0258	1143	1569	0426	0795	0952	0157	0348	0440	0092
2.	1960	1680	-280	1803	1310	-493	0235	0538	0213	1588	0788	-800
3.	1480	2214	0734	1140	1904	0764	0592	0886	0294	0594	0952	0390
14.	0652	2340	1688	0469	1661	1192	0241	0865	0624	0235	0234	-001
15.	1645	2256	0611	1365	1850	0485	0724	1038	0314	0576	0519	-057
16.	0703	2025	1322	0562	1721	1159	0400	1438	1038	0105	0243	0138
17.	1755	1943	0188	1597	1865	0268	1193	1438	0245	0386	0427	0041
18.	2772	3071	0299	1663	2027	0364	0915	1966	1051	0499	0350	-0149
X	1324.5	2128	803.4	1017.3	1735.47	718.17	571.9	1091.2	519.3	389.9	502.9	113
P			<0.001			<0.001			<0.001			>0.05

Normal ranges for lymphocytes, T11, T4 and T8 established on 60 males and females by EHC - Dallas. (15)

TABLE 3

Patients with Normal T-B Lymphocyte Numbers and Normal CMI Response

Patient	Numbers of lymphocytes, T and B cells/mm^3 Total 1400 to 4200	T11 1269 to 2650	T4 0670 to 1800	T8 0333 to 1070	T4:T8 001 to 2.7	BI 082 to 479	Cell mediated immune response # Positive Reactions	Sum Reaction Size (mm)	Clinical Status
B.D.	3196	2650	1502	0927	01.6	479	ND	ND	no change
E.J.	2676	2087	1340	0721	01.9	283	4	25.2	no change
E.M.	3071	2072	1966	0350	05.6	215	3	18.0	improved
HA.S.	3087	2686	1852	0864	02.1	463	5	17.5	improved
H.S.	2460	2066	1156	0861	01.3	394	6	35.5	improved
HE.S.	2650	2014	1193	0795	01.5	371	4	18.5	improved
J.W.	2193	1167	0899	0592	01.5	219	5	21.0	improved
M.R.	3083	ND	1337	0760	01.8	ND	4	20.0	improved
M.L.	1914	1569	0952	0440	02.2	230	4	17.5	improved
R.S.	1645	1365	0724	0579	01.3	165	3	13.5	improved
S.M.	1974	1579	1046	0474	02.2	257	5	25.0	no change
S.G.	2000	1440	0640	0600	01.1	360	5	17.0	improved
SP.M.	1880	1372	0827	0414	02.0	150	6	26.0	improved
B.S.	2668	2214	1174	0694	01.7	107	2	15.0	

inducer factor activity. This vie [redacted] ...e availability of TF "acceptor cells" can only be [redacted]mmodated cautiously pending further elucidation of regulatory mechanisms acting on the presumed TF acceptor. For now it would appear that the "DH-potential" cell (presumably a naive lymphocyte) is converted to an antigen responsive state that acquirës the immunocompetence of natively sensitive cells in vivo and in vitro (11).

In our studies [redacted]ose of Fudenberg, et.al. (21) (who treated a patient [redacted]...scoid lupus), dramatic increases in CMI response to various bacterial and mycotic antigens and elevation of numbers of T and T helper lymphocytes were observed. These responses were associated with clinical relief from certain environmentally-incited symptoms, suggesting the utility of TF in the treatment of such diseases.

TABLE 4

Patients with Abnormal T-B Lymphocyte Numbers and Abnormal CMI Response

	numbers of lymphocytes T and B cells/mm^3						cell mediated immune response		
Patient	Total 1400 to 4200	T11 1260 to 2650	T4 670 to 1800	T8 333 to 1070	T4:T8 1 to 2.7	B1 82 to 477	# positive reactions	Sum reaction size (mm)	Clinical Status
B.S.	1602	0849	465	208	2.2	160	1	4.0	improved
C.C.	1740	1183	644	522	1.2	174	0	0	improved
E.D.	1050	0998	410	462	0.9	105	ND	ND	improved
E.M.	0976	0625	439	185	2.4	137	0	0	improved
B.V.	1700	0960	528	408	1.3	096	2	13.0	improved
H.M.	0728	0648	495	102	4.8	073	1	3.0	improved
H.S.	1400	0980	588	392	1.5	084	3	12.0	improved
H.D.	1840	1118	541	541	1.0	198	0	0	improved
HE.D	1590	1113	652	413	1.6	080	2	12.0	improved
J.M.	0775	0636	450	163	2.8	132	0	0	improved
L.D.	1368	1259	889	315	2.8	ND	0	0	no change
M.M.	4056	3488	1541	1906	0.8	852	0	0	improved
O.S.	1906	1803	235	1588	0.14	32	1	3.5	improved
R.M.	0652	0469	241	235	1.0	124	1	7.5	improved
S.M.	0994	0815	596	209	3.0	129	1	2.0	improved
M.J.	1175	0893	529	294	1.8	200	0	0	no change
D.J.	1352	1190	730	406	1.8	203	2	13.0	improved

TABLE 5

Patients with Normal T-B Lymphocyte Numbers and Abnormal CMI Response

	numbers of lymphocytes, T and B cells/mm3						cell mediated immune response		
Patients	Total 1400 to 4200	T11 1260 to 2650	T4 670 to 1800	T8 333 to 1070	T4:T8 1 to 2.7	B1 82 to 477	# positive reactions	Sum reaction size (mm)	Clinical Status
K.S.	1885	1433	0905	0528	1.7	320	0	00	no change
L.A.	1998	1419	1039	0380	2.7	220	2	06	improved
L.B.	1560	1201	0671	0468	1.4	203	3	10	improved
M.A.	2257	1715	1129	0564	2.0	271	1	07	no change
O.C.	1624	1283	0828	0487	1.7	211	1	04	improved
R.R.	2790	1981	1367	0614	2.2	558	1	03	improved
S.T.	1404	1095	0702	0323	323	351	0	00	improved
SC.I.	3432	2540	1544	1064	1.5	515	0	00	improved
W.F.	1755	1597	1193	0386	3.1	ND	1	01	improved
W.S.	2220	1998	0997	0844	1.2	244	1	06	improved
B.L.	2356	1814	0895	0707	1.3	118	2	10	improved
B.P.	2580	2064	1032	0851	361	361	1	02	improved
C.C.	2948	2211	1268	0796	1.6	354	0	00	no change

TABLE 6
Patients with Abnormal T-B Lymphocytes and Normal CMI Response

	number of lympocytes T and B cells/mm3				cell mediated immune response				
Patients	Total 1400 to 4200	T11 1260 to 2650	T4 670 to 1800	T8 333 to 1070	T4:T8 1 to 2.7	B1 82 to 477	# positive reactions	Sum reaction size (mm)	Clinical Status
K.M.	1344	1196	524	605	0.9	ND	3	04.0	no change
K.K.	1540	1093	662	416	1.6	154	5	17.5	no change
N.S.	1140	0969	422	308	1.4	046	4	16.0	improved

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